PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/47, 31/435

A1

(11) International Publication Number: WO 98/17279

(43) International Publication Date: 30 April 1998 (30.04.98)

(21) International Application Number: PCT/US97/19990

(22) International Filing Date: 24 October 1997 (24.10.97)

(30) Priority Data:

60/029,301	25 October 1996 (25.10.96)	US
60/045,331	1 May 1997 (01.05.97)	US

(71) Applicant: MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventors: TOMAI, Mark, A.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). HAMMERBECK, David, M.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). SWINGLE, Karl, F.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: RINGSRED, Ted, K. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMMUNE RESPONSE MODIFIER COMPOUNDS FOR TREATMENT OF TH2 MEDIATED AND RELATED DISEASES

(57) Abstract

Immune response modifier compounds – imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines – are useful for the treatment of TH2 mediated diseases by administering a therapeutically effective amount of such compounds in order to inhibit TH2 immune response, suppress IL-4/IL-5 cytokine induction and eosinophilia, as well as enhance TH1 immune response.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Immune Response Modifier Compounds for Treatment of TH2 Mediated and Related Diseases

BACKGROUND OF THE INVENTION

The present invention relates to the use of immunomodifying imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines to inhibit T helper-type 2 (TH2) immune response and thereby treat TH2 mediated diseases. It also relates to the ability of these compounds to inhibit induction of interleukin (IL)-4 and IL-5, and to suppress eosinophilia.

Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, and 1,2-bridged imidazoquinoline amine compounds have demonstrated potent immunostimulating, antiviral and antitumor (including anticancer) activity, and have also been shown to be useful as vaccine adjuvants to enhance protective immune system response to vaccines. These compounds are hereinafter sometimes collectively referred to as the "IRM" (immune response modifier) compounds of the invention. Such compounds are disclosed in, for example, U.S. Patents 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 5,352,784, 5,494,916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, and 5,525,612, WO 93/20847, and European Patent Application 90.301776.3, wherein their immunostimulating, antiviral and antitumor activities are discussed in detail, and certain specific diseases are identified as being susceptible to treatment therewith, including basal cell carcinoma, eczema, essential thrombocythaemia, hepatitis B, multiple sclerosis, neoplastic diseases, psoriasis, rheumatoid arthritis, type I herpes simplex, type II herpes simplex, and warts. One of these IRM compounds, known as imiquimod, has been commercialized in a topical formulation, Aldara™, for the treatment of anogenital warts associated with human papilloma virus.

The mechanism for the antiviral and antitumor activity of these IRM compounds is thought to be due in substantial part to enhancement of the immune response due to induction of various important cytokines (e.g., interferons, interleukins, tumor necrosis factor, etc.). Such compounds have been shown to stimulate a rapid release of certain monocyte/macrophage-derived cytokines and are also capable of stimulating B cells to secrete antibodies which play an important role in these IRM compounds' antiviral and antitumor activities. One of the predominant immunostimulating responses to these compounds is the induction of interferon (IFN)-α production, which is believed to be very important in the acute antiviral and antitumor activities seen. Moreover, up regulation of other cytokines such as, for example, tumor necrosis factor (TNF), IL-1 and IL-6 also have potentially beneficial activities and are believed to contribute to the antiviral and antitumor properties of these compounds.

However, there are many diseases where the immune system itself actually appears to play a significant role in mediating the disease (i.e., the immune system action takes part in actually

causing the disease or an inappropriate type of immune response prevents the correct response from irradicating the disease). Many such diseases are thought to involve a pathologic or inappropriate immune response by the humoral branch of the immune system, which is associated with TH2 cell activity (as opposed to TH1 cell mediated immunity).

The humoral/TH2 branch of the immune system is generally directed at protecting against extracellular immunogens such as bacteria and parasites through the production of antibodies by B cells; whereas the cellular/TH1 branch is generally directed at intracellular immunogens such as viruses and cancers through the activity of natural killer cells, cytotoxic T lymphocytes and activated macrophages. TH2 cells are believed to produce the cytokines IL-3, IL-4, IL-5, and IL-10, which are thought to stimulate production of IgE antibodies, as well as be involved with recruitment, proliferation, differentiation, maintenance and survival of eosinophils (i.e., leukocytes that accept an eosin stain), which can result in eosinophilia. Eosinophilia is a hallmark of many TH2 mediated diseases, such as asthma, allergy, and atopic dermatitis.

The interplay and importance of various aspects of immune system response, including interaction between TH1 and TH2 cell cytokines is discussed in WO 97/2688. Although WO 97/2688 is specifically concerned with the effects of a particular antiviral compound known as Ribavirin®, which is dissimilar to the IRM compounds of the present invention, it nonetheless illustrates some of the complex and unpredictable effects of drug compounds on the immune system.

SUMMARY OF THE INVENTION

It has now been found that in addition to their immunostimulatory, antiviral/antitumor effect on the immune system, the IRM compounds of the present invention—imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines—are also extremely useful for down regulating certain key aspects of the immune response. Specifically, the IRM compounds of the present invention have been found to and inhibit TH2 immune response (in addition to enhancing TH1 immune response). This is extremely important for treating TH2 mediated diseases where an inappropriate TH2 response is causing the disease or preventing eradication of the disease by TH1 response. Thus, when administered in a therapeutically effective amount these IRM compounds can be used for treating TH2 mediated diseases.

An apparently related effect of the present IRM compounds is to inhibit the induction of IL-4, IL-5, and perhaps other cytokines, which thereby allows for treatment of diseases associated with these cytokines. A further important and surprising effect of these compounds is the suppression of eosinophils, which allows for treatment of eosinophilia and related diseases.

Some diseases that are thought to be caused/mediated in substantial part by TH2 immune response, IL-4/IL-5 cytokine induction, and/or eosinophilia (and accordingly responsive to

treatment by administering a therapeutically effective amount of the present IRM compounds) include asthma, allergic rhinitis, systemic lupus erythematosis, Ommen's syndrome (hypereosinophilia syndrome), certain parasitic infections, for example, cutaneous and systemic leishmaniasis, toxoplasma infection and trypanosome infection, and certain fungal infections, for example candidiasis and histoplasmosis, and certain intracellular bacterial infections, such as leprosy and tuberculosis. These are examples of non-viral and non-tumor, TH2 mediated diseases for which effective treatment with the present IRM compounds clearly could not have been predicted. Additionally, it should also be noted that diseases having a viral or cancer related basis, but with a significant TH2 mediated pathology can also be beneficially treated with the IRM compounds of the present invention. Particularly preferred uses of the IRM compounds of the present invention are for the treatment of diseases associated with eosinophilia, such as asthma and allergic rhinitis.

The present IRM compounds may be administered via any suitable means, for example, parenterally, transdermally, and orally. One preferred delivery route is via a topical gel or cream formulation. For treatment of asthma and allergic rhinitis, it is preferred to deliver the IRM compound via oral and/or nasal inhalation from a metered dose inhaler.

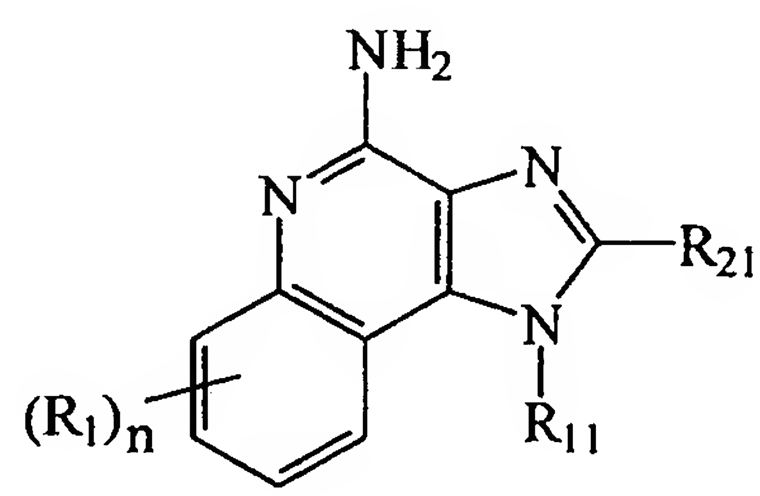
Particularly preferred IRM compounds include 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol and 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (known as Imiquimod).

Finally, it should be noted that the diseases identified as being treatable in the published patents referred to above in the background (U.S. Patents 4,689,338, 5,389,640, 5,268,376, 4,929,624, 5,266,575, 5,352,784, 5,494, 916, 5,482,936, 5,346,905, 5,395,937, 5,238,944, and 5,525,612, WO 93/20847, and European Patent Application 90.301776.3) are generally either viral/tumor based or, if not, are thought not to be TH2 mediated diseases. One exception is eczema, which, although a TH2 mediated disease, is believed to have been identified due to a susceptibility to treatment with interferon (which was then understood to be the main cytokine response induced by the present compounds). There was, however, no recognition at the time that any TH2, IL-4/5, or eosinophilia suppressing ability of the present IRM compounds could be used for treating eczema.

DETAILED DESCRIPTION

Preferred IRM Compounds

As noted above, many of the imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, and 1,2-bridged imidazoquinoline amine IRM compounds of the present invention have demonstrated significant immunomodulating activity. Preferred immune response modifier compounds include 1H-imidazo[4,5-c]quinolin-4-amines defined by one of Formulas I-V below:



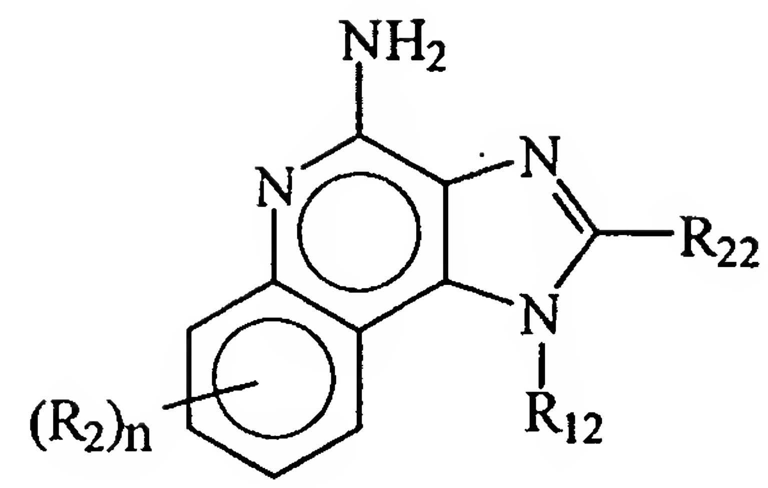
I

wherein

R_{11} is selected from the group consisting of alkyl of one to about ten carbon atoms, hydroxyalkyl of one to about six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than six carbon atoms;

R_{21} is selected from the group consisting of hydrogen, alkyl of one to about eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and

each R_1 is independently selected from the group consisting of alkoxy of one to about four carbon atoms, halogen, and alkyl of one to about four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_1 groups together contain no more than six carbon atoms;



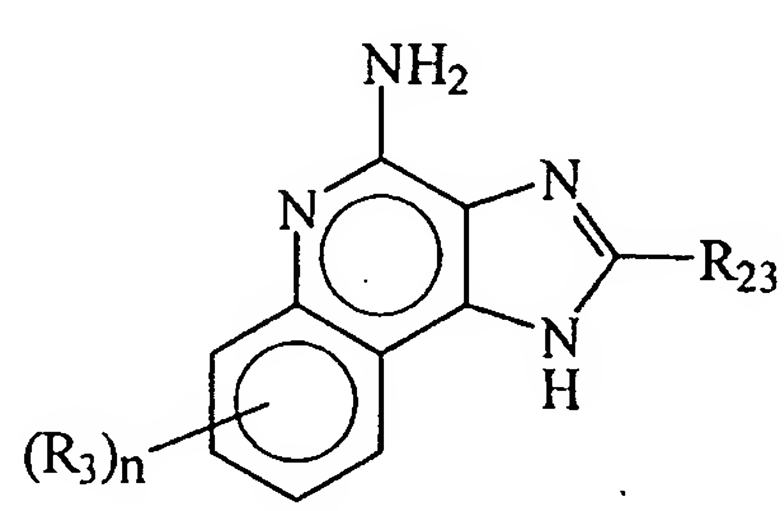
II

wherein

R_{12} is selected from the group consisting of straight chain or branched chain alkenyl containing two to about ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to about ten carbon atoms, wherein the substituent is selected from the group consisting of straight chain or branched chain alkyl containing one to about four carbon atoms and cycloalkyl containing three to about six carbon atoms; and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; and

R_{22} is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to about eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of straight chain or branched chain alkyl containing one to about four carbon atoms, straight chain or branched chain alkoxy containing one to about four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each R_2 is independently selected from the group consisting of straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_2 groups together contain no more than six carbon atoms;

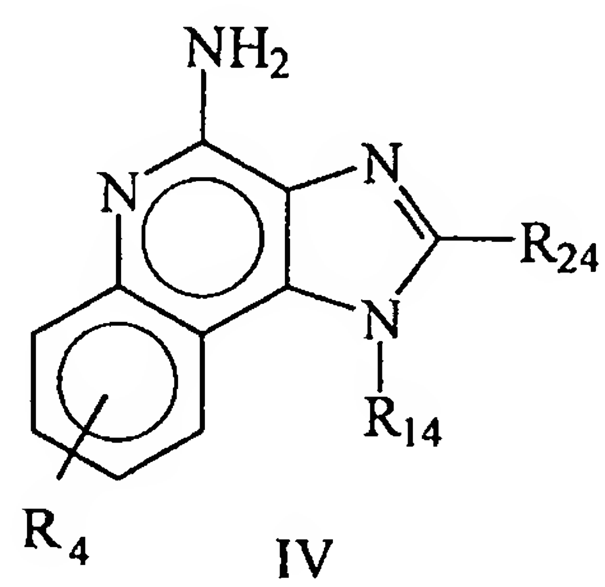


III

wherein

R_{23} is selected from the group consisting of hydrogen, straight chain or branched chain alkyl of one to about eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of straight chain or branched chain alkyl of one to about four carbon atoms, straight chain or branched chain alkoxy of one to about four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each R_3 is independently selected from the group consisting of straight chain or branched chain alkoxy of one to about four carbon atoms, halogen, and straight chain or branched chain alkyl of one to about four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_3 groups together contain no more than six carbon atoms;



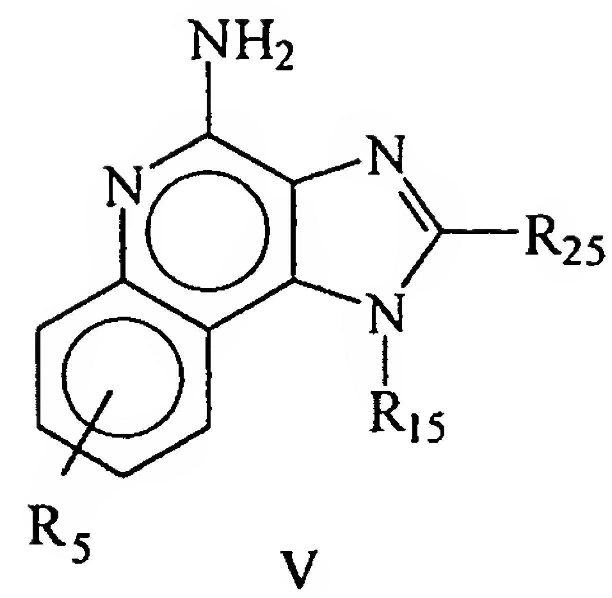
IV

wherein

R_{14} is -CHR_xR_y wherein R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to about four carbon atoms, hydroxyalkoxy of one to about four carbon atoms, 1-alkynyl of two to about ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and hydroxyalkyl of one to about four carbon atoms;

R_{24} is selected from the group consisting of hydrogen, alkyl of one to about four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen; and

R_4 is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms;

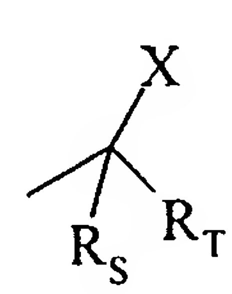


V

wherein

R_{15} is selected from the group consisting of: hydrogen; straight chain or branched chain alkyl containing one to about ten carbon atoms and substituted straight chain or branched chain alkyl containing one to about ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to about six carbon atoms and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; straight chain or branched chain alkenyl containing two to about ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to about ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to about six carbon atoms and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; hydroxyalkyl of one to about six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

R_{25} is



wherein

R_S and R_T are independently selected from the group consisting of hydrogen, alkyl of one to about four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from

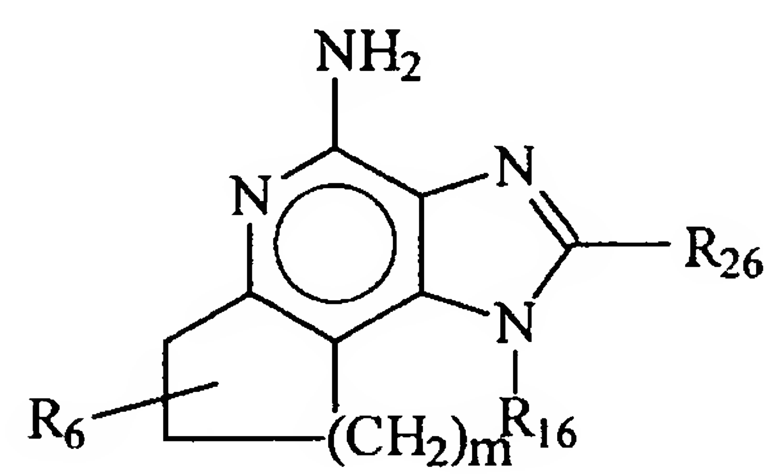
the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen;

X is selected from the group consisting of alkoxy containing one to about four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms, hydroxyalkyl of one to about four carbon atoms, haloalkyl of one to about four carbon atoms, alkylamido wherein the alkyl group contains one to about four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to about four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one to about four carbon atoms; and

R_5 is selected from the group consisting of hydrogen, straight chain or branched chain alkoxy containing one to about four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to about four carbon atoms;

or a pharmaceutically acceptable salt of any of the foregoing.

Preferred 6,7 fused cycloalkylimidazopyridine amine IRM compounds are defined by Formula VI below:



VI

wherein m is 1, 2, or 3;

R_{16} is selected from the group consisting of hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to about ten carbon atoms and substituted straight chain or branched chain alkyl containing one to about ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to about six carbon atoms and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; fluoro- or chloroalkyl containing from one to about ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to about ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to about ten carbon atoms, wherein the substituent is selected from the group consisting of cycloalkyl containing three to about six carbon atoms and cycloalkyl containing three to about six carbon atoms substituted by straight chain or branched chain alkyl containing one to about four carbon atoms; hydroxyalkyl of one to about six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the

alkyl moiety contains one to about six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

and $-CHR_xR_y$

wherein

R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to about four carbon atoms, hydroxyalkoxy of one to about four carbon atoms, 1-alkynyl of two to about ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from the group consisting of hydroxy and hydroxyalkyl of one to about four carbon atoms,

R_{26} is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to about eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to about six carbon atoms, morpholinomethyl, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from the group consisting of methyl, methoxy, and halogen; and

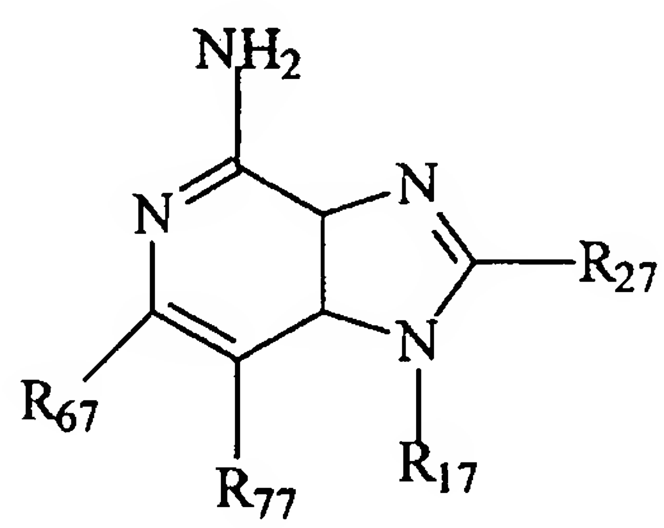
$-C(R_S)(R_T)(X)$ wherein R_S and R_T are independently selected from the group consisting of hydrogen, alkyl of one to about four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen;

X is selected from the group consisting of alkoxy containing one to about four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about four carbon atoms, haloalkyl of one to about four carbon atoms, alkylamido wherein the alkyl group contains one to about four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to about four carbon atoms, azido, alkylthio of one to about four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to about four carbon atoms, and

R_6 is selected from the group consisting of hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to about four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to about four carbon atoms and at least one fluorine or chlorine atom;

and pharmaceutically acceptable salts thereof.

Preferred imidazopyridine amine IRM compounds are defined by Formula VII below:



VII

wherein

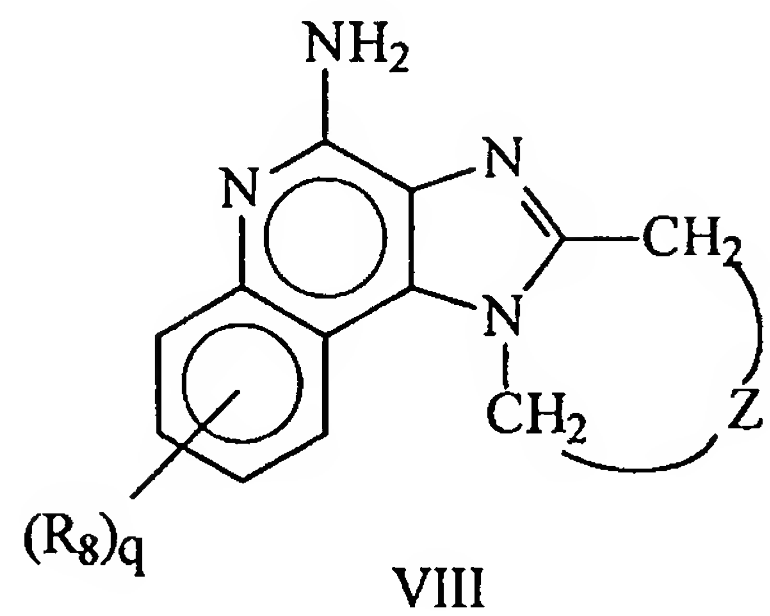
R_{17} is selected from the group consisting of hydrogen; $-CH_2R_W$ wherein R_W is selected from the group consisting of straight chain, branched chain, or cyclic alkyl containing one to about ten carbon atoms, straight chain or branched chain alkenyl containing two to about ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to about six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about six carbon atoms, and phenylethyl; and $-CH=CR_ZR_Z$ wherein each R_Z is independently straight chain, branched chain, or cyclic alkyl of one to about six carbon atoms;

R_{27} is selected from the group consisting of hydrogen, straight chain or branched chain alkyl containing one to about eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to about six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to about four carbon atoms and the alkyl moiety contains one to about six carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety selected from the group consisting of methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to about four carbon atoms;

R_{67} and R_{77} are independently selected from the group consisting of hydrogen and alkyl of one to about five carbon atoms, with the proviso that R_{67} and R_{77} taken together contain no more than six carbon atoms, and with the further proviso that when R_{77} is hydrogen then R_{67} is other than hydrogen and R_{27} is other than hydrogen or morpholinoalkyl, and with the further proviso that when R_{67} is hydrogen then R_{77} and R_{27} are other than hydrogen;

and pharmaceutically acceptable salts thereof.

Preferred 1,2-bridged imidazoquinoline amine IRM compounds are defined by Formula VIII below:



VIII

wherein

Z is selected from the group consisting of:

$-(CH_2)_p-$ wherein p is 1 to 4;

$-(CH_2)_a-C(R_DR_E)(CH_2)_b-$, wherein a and b are integers and a+b is 0 to 3, R_D is hydrogen or alkyl of one to four carbon atoms, and R_E is selected from the group consisting of alkyl of one to four carbon atoms, hydroxy, $-OR_F$ wherein R_F is alkyl of one to four carbon atoms, and $-NR_GR'_G$ wherein R_G and R'_G are independently hydrogen or alkyl of one to four carbon atoms; and

$-(CH_2)_a-(Y)-(CH_2)_b-$ wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or $-NR_J-$ wherein R_J is hydrogen or alkyl of one to four carbon atoms;

and wherein q is 0 or 1 and R_8 is selected from the group consisting of alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen,

and pharmaceutically acceptable salts thereof.

The compounds recited above are disclosed in the patents and applications noted above in the Background.

The substituents R_{11} - R_{17} above are generally designated "1-substituents" herein. The preferred 1-substituents are alkyl containing one to six carbon atoms and hydroxyalkyl containing one to six carbon atoms. More preferably the 1- substituent is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

The substituents R_{21} - R_{27} above are generally designated "2-substituents" herein. The preferred 2-substituents are hydrogen, alkyl of one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, and hydroxyalkyl of one to four carbon atoms. More preferably the 2-substituent is hydrogen, methyl, butyl, hydroxymethyl, ethoxymethyl or methoxyethyl.

In instances where n can be zero, one, or two, n is preferably zero or one.

The amounts of these IRM compounds that will be therapeutically effective in a specific situation will of course depend on such things as the activity of the particular compound, the mode of administration, and the disease being treated. As such, it is not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine

appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to these compounds, and routine testing.

Immune System Mechanisms

Recent evidence indicates that the immune system can be broken down into two major arms, the humoral and cellular arms. The humoral arm is important in eliminating extracellular pathogens such as bacteria and parasites through production of antibodies by B cells. On the other hand, the cellular arm is important in the elimination of intracellular pathogens such as viruses through the activity of natural killer cells, cytotoxic T lymphocytes and activated macrophages. In recent years it has become apparent that these two arms are activated through distinct T helper cell (TH) populations and their distinct cytokine production profiles. T helper type 1 (TH1) cells are believed to enhance the cellular arm of the immune response and produce predominately the cytokines IL-2 and IFN-γ; whereas, T helper 2 (TH2) cells are believed to enhance the humoral arm of the immune response and produce cytokines, such as interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5) and granulocyte-macrophage colony-stimulating factor (GM-CSF). In the TH2 case, IL-3, IL-5 and GM-CSF are thought to stimulate eosinophilopoiesis. In addition, IL-5 facilitates terminal differentiation and cell proliferation of eosinophils and promotes survival, viability and migration of eosinophils, while IL-4 stimulates production of antibodies of the IgE class. IgE is an important component in allergies and asthma. IL-5 may also prime eosinophils for the subsequent actions of other mediators.

In contrast, the TH1 cytokines, IL-2 and IFN-γ, are important in activating macrophages, NK cells and CTL (cytotoxic T lymphocytes). IFN-γ also stimulates B cells to secrete specifically cytophilic antibody for the elimination of virally-infected cells. Interestingly, IFN-α, a macrophage-derived cytokine has been shown to antagonize TH2-type responses. IFN-α also appears to inhibit the proliferation and cytokine production of TH2 cells and enhances IFN-γ production by TH1 cells. In addition, IFN-α also appears to inhibit IgE production and antigen-induced increases in IL4 mRNA levels.

TH1 stimulation versus TH2 down regulation

IRM compounds of the present invention have been shown in a number of models to augment cell mediated immunity, which is consistent with stimulation of TH1 cells. Surprisingly, in models of eosinophilia (TH2/humoral immune mediated process) these compounds actually inhibit the eosinophilia. Further studies indicate that the way in which these compounds are achieving this is in part by their ability to inhibit TH2 cell production of the cytokine IL-5. We have shown in both in vitro and in vivo models, inhibition of IL-5 production by imidazoquinolines. For example, as shown in Table 1, an exemplary IRM compound 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol dramatically inhibits IL-5

production in spleen cell cultures stimulated with antigen. Spleen cells from OVA-sensitized CFW mice ($2x10^6$/ml) were cultured for 96 hr with OVA (100μg/ml). Some cultures also received this IRM compound over a range of concentrations. Culture supernatants were collected and analyzed by ELISA (Endogen) for IL-5. Results are presented as the mean of triplicate cultures±SEM. IL-5 concentration is in pg/ml.

Table 1

Inhibition of Mouse Spleen Cell Production of IL-5

Treatment	IRM Compound Concentration	IL-5 Concentration (pg/ml)
OVA alone		240±20
OVA + IRM Compound	10μg/ml	12±2
OVA + IRM Compound	1μg/ml	22±3
OVA + IRM Compound	0.1μg/ml	25±8
OVA + IRM Compound	0.01μg/ml	125±46
Medium		57±27

As can be seen from Table 1, concentrations of IRM compound as low as 0.01 μg/ml inhibit IL-5 production by greater than 60%; whereas, higher concentrations inhibit IL-5 production by 100%.

In vivo, the exemplary IRM compound 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol was shown to inhibit antigen induced IL-5 production in a dose dependent manner, as shown in Table 2. CFW male mice were sensitized with OVA as described above. 14 days after the last sensitization animals were challenged with 100 μg OVA sc. Some animals received the free-base of 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol po either at the same time of OVA challenge or 24 hrs before. Serum was collected 7 hrs after OVA and analyzed for IL-5 and IFN-γ concentrations. Results are expressed as the mean cytokine concentration ±SEM.

Table 2
Effects of IRM Compounds on IL-5 and IFN-γ Production

IRM Compound Dose (mg/kg)	Cytokine Concentration (pg/mL) ±SEM	
	-24 hr IL-5 (pg/mL)	0 hr IL-5 (pg/mL)
0.01	78	96
0.1	49	62
1.0	38	40
10.0	8	29
Sen. Control	213	270
Normal Control	1	1

It can thus be seen that 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol was active when given either at the same time of antigen challenge or when given a day before antigen. Doses as low as 0.01 mg/kg inhibited IL-5 production by at least 65%.

One common feature of many TH2 mediated diseases is an accumulation of eosinophils, referred to as eosinophilia. For example, chronic pulmonary inflammation involving eosinophil infiltration is a characteristic hallmark feature of bronchial asthma. Increased numbers of eosinophils have been observed in blood, bronchoalveolar lavage fluid and pulmonary tissue in patients with asthma, but the mechanism(s) responsible for their recruitment into and regulation within pulmonary tissues undergoing allergic or pro-inflammatory reactions has not been fully understood. Mediators and cytokines from T-lymphocytes and effector cells such as basophils, mast cells, macrophages and eosinophils have been implicated in enhancing cell maturation, chemotaxis and activation of eosinophils. Evidence suggests that an association exists between the immune system, especially $CD4^+$ T cells, and eosinophils and eosinophil recruitment. Studies in asthmatics and in animal models of allergic pulmonary responses support this notion with the evidence of close correlations between the relative numbers of T cells and activated eosinophils in the airways. The importance of T-lymphocyte in eosinophil recruitment is strengthened by studies with T cell-selective immunosuppressive agents like cyclosporin A, FK506 and cyclophosphamide. These agents have been shown to reduce eosinophilia. Immunostimulants on the other hand have generally not been shown to clearly reduce eosinophilia. However, this may be a reflection on how these immunostimulants are affecting the immune system.

The following three sets of studies clearly indicate that the IRM compounds of the present invention can be used to suppress eosinophilia.

The first set of studies evaluate the IRM compound 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol for its ability to inhibit antigen-induced eosinophilia in the lung after aerosol challenge with antigen. Results in Table 3 show that 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol at 1 mg/kg is capable of

inhibiting antigen-induced eosinophilia in the lung of mice by 78% when given 15 minutes prior to antigen challenge. Concentrations of IL-4 were reduced in the BAL of these mice by 43% when compared to animals receiving antigen alone. Also, the IRM compound induced inhibition of eosinophilia correlated with a significant inhibition in BAL concentrations of IL-5, which were reduced by 78%. CFW mice were sensitized on day 0 with 10 μg of ovalbumin (OVA) ip in 1% alum and then boosted 7 days later with the same regimen. Fourteen days after boosting animals were dosed by nebulization for 30 minutes using a 1% OVA solution. This was repeated on days 17 and 20. Twenty-four hours after the final nebulized dose animals were sacrificed and bronchoalveolar lavage (BAL) was performed using 1.0 ml of PBS containing 1% fetal bovine serum. BAL was stored at -70°C before analyzed. Lungs were then removed and placed in 0.5% cetrimide, 0.05 M KH2PO4 for homogenization of 4 X 30 seconds with 30 second cooling intervals between on ice. Centrifugation was then done at 1300 rpm (400 X g) for 30 minutes at 4C. Pellet was collected and resuspended in 4 ml 0.5 % cetrimide, 0.05 M KH2PO4 buffer. Samples were then frozen until sonication and the EPO assessment. This was followed by sonication for 3 X 15 seconds with 30 second intervals on ice.

An EPO (eosinophil peroxidase, an eosinophil protein used as a marker of eosinophil presence) assay consisted of determining the levels of EPO in the lung tissue (or supernatant of BAL fluid) from each individual guinea pig sample. 50 ul of the "sample solution" consisting of 375 ul PBS (pH 7, RT) + 25 ul 0.05 M TRIS-HCL containing 2 % Triton (pH 8, RT) + 50 ul of sonicated lung lobe was added to 860 ul 0.05 M TRIS-HCL containing 0.1 % Triton (pH 8, RT) in combination with 8.5 ul mM 0-phenylenediaminedihydrochloride (OPD). To start the reaction, 1 ul of 30 % hydrogen peroxide was added to the cuvette. The optical density reading was measured spectrophotometrically over a 4 minute time interval at 490 nm in a Beckman Du-64 spectrophotometer.

BAL were analyzed by ELISA (Endogen) for IL-5 and IL-4 concentrations with data being presented as the average from 11 animals ± SEM. Results are presented as the mean of triplicate cultures±SEM. IL-5 concentration is in pg/ml.

Table 3
Inhibition of Antigen-induced Lung Eosinophilia, IL-5 and IL-4

Treatment	EPO Concentration in Lung (ABS)	IL-5 Concentration in BAL (pg/ml)	IL-4 Concentration in BAL (pg/ml)
Non sensitized Control	258±28	0.8±0.3	30±3
Antigen Sensitized	600±87 (100)	59±18 (100)	70±10 (100)
IRM Compound + Antigen	352±30 (78)*	13±2 (78)*	53±8 (42)

*=Significant difference from ovalbumin control group at α=0.05

The second set of studies evaluated the two IRM compounds 4-amino-α,α.-2-trimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (Cmpd 1) and 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (Cmpd 2) for their ability to inhibit sephadex-induced eosinophilia in the lung intravenous sephadex challenge . Results in Table 4 show that oral administration or intratracheal instillation of IRM Cmpd Ex. 1 at ≥0.7mg/kg and oral administration of Cmpd 2 at ≥0.01 mg/kg are capable of inhibiting sephadex-induced eosinophilia in the lung of rats when given 60 minutes prior to challenge. A maximum inhibition of 95% occurred with Cmpd 1 and 87% occurred with Cmpd 2.

Male, Sprague Dawley rats were injected on day 0 with sephadex G-200 particles in a lateral tail vein (0.5 mg/rat). On days 14-16, the rats were lightly anesthetized with halothane and subsequently dosed with either drug or vehicle (1.0 mg/kg, orally) 24 hours and 1 hour before a second sephadex challenge on day 14. A booster of Sephadex G-200 particles was administered intravenously in a lateral tail vein (0.5 mg/rat) at 1 hour post-drug (i.e., following either drug or vehicle) on day 14 only. The animals are sacrificed on day 17 at 72 hrs. post-sephadex dosing by lethal injection of sodium pentobarbital (100-125 mg/kg, ip). Lungs were exanguinated, lavaged, and removed. They were then placed in 0.5 % cetrimide, 0.05 M KH2PO4 for homogenization of 4 X 30 seconds with 30 second cooling intervals between on ice. Centrifugation was then done at 1300 rpm (400 X g) for 30 minutes at 4C. Pellet was collected and resuspended in 4 ml 0.5 % cetrimide, 0.05 M KH2PO4 buffer. Samples were then frozen until sonication and the EPO assessment. This was followed by sonication for 3 X 15 seconds with 30 second intervals on ice.

The EPO (eosinophil peroxidase, an eosinophil protein used as a marker of eosinophil presence) assay consisted of determining the levels of EPO in the lung tissue (or supernatant of BAL fluid) from each individual rat sample. 50 ul of the "sample solution" consisting of 375 ul PBS (pH 7, RT) + 25 ul 0.05 M TRIS-HCL containing 2 % Triton (pH 8, RT) + 50 ul of sonicated lung lobe was added to 860 ul 0.05 M TRIS-HCL containing 0.1 % Triton (pH 8, RT) in combination with 8.5 ul mM 0-phenylenediaminedihydrochloride (OPD). To start the reaction, 1 ul of 30 % hydrogen peroxide was added to the cuvette. The optical density reading was measured spectrophotometrically over a 4 minute time interval at 490 nm in a Beckman Du-64 spectrophotometer.

Table 4

Inhibition of Sephadex-induced Lung Eosinophilia in Rats

Treatment	Drug mg/k	EPO Concentration in the Lung[b,c] ($\chi \pm SE$)	% Inhibition
Group 1:			
Cmpd 1 Intratracheal Instillation			
Non-Sephadex Control	0.0	0.0923 ± 0.017	
Sephadex Challenged	0.0	0.5456 ± 0.085	
Drug + Sephadex Challenged	0.03	0.7107 ± 0.129	0%
	0.1	0.5030 ± 0.089	9%
	0.3	0.3440 ± 0.201	44%
	0.7	0.1967 + 0.080*	77%
Group 2:			
Cmpd 1 Oral Administration			
Non-Sephadex Control	0.0	0.0390 ± 0.008	
Sephadex Challenged	0.0	0.3453 ± 0.100	
Drug + Sephadex Challenged	0.1	0.4240 ± 0.138	0%
	0.7	0.1497 ± 0.030*	64%
	1.0	0.0780 ± 0.039*	87%
	5.0	0.0790 + 0.030*	87%
	30.0	0.0550 + 0.013*	95%
Group 3:			
Cmpd 2 Oral Administration			
Non-Sephadex Control	0.0	0.1072 ± 0.020	
Sephadex Challenged	0.0	0.6738 ± 0.100	
Drug + Sephadex Challenged	0.001	0.6775 ± 0.140	0%
	0.01	0.4908 ± 0.070*	32%
	0.1	0.2000 ± 0.060*	84%
	1.0	0.1824 + 0.060*	87%

*= Significant difference from ovalbumin control group at α=0.05

The third set of studies evaluated 4-amino-α,α,-2-trimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (Cmpd 1) and 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (Cmpd 2) for their ability to inhibit ovalbumin-induced eosinophilia in the lung aerosol antigen challenge . Results in Table 5 show that intraperitoneal administration or aerosol inhalation of Cmpd 1 at 0.01 mg/kg and oral administration of Cmpd 2 at 0.01 mg/kg are capable of inhibiting ovalbumin-induced eosinophilia in the lung of guinea pigs when given either 15 or 60 minutes prior to challenge, respectively. A maximum inhibition of 92% occurred with IRM Cmpd 1 and 96% occurred with IRM Cmpd 2. In the guinea pig, these two imidazoquinoline compounds produce approximately equivalent effects on ovalbumin-induced lung eosinophilia.

Male Hartley guinea pigs (~250-500 g), sensitized to ovalbumin (50 mg/kg, ip, greater than or equal to 14 days) were dosed with chlorpheniramine (5 mg/kg, ip) and drug or vehicle intratracheally (or by another route) at 15 minutes pre-challenge. Animals were placed inside an inverted dessicator jar which was placed onto a plexiglass platform. The platform allowed for aerosolization of H_2O or ovalbumin (50 mg/ml) for 5 minutes via a No. 40 DeVilbiss nebulizer, and for providing a constant flow of air into the chamber from a continuous air source. Animals were

sacrificed at 24 hrs. post-challenge by lethal injection of sodium pentobarbital (100-125 mg/kg, ip). Lungs were exanguinated, lavaged, and removed. They were then placed in 0.5 % cetrimide, 0.05 M KH2PO4 for homogenization of 4 X 30 seconds with 30 second cooling intervals between on ice. Centrifugation was then done at 1300 rpm (400 X g) for 30 minutes at 4C. Pellet was collected and resuspended in 4 ml 0.5 % cetrimide, 0.05 M KH2PO4 buffer. Samples were frozen until assayed. This was followed by sonication for 3 X 15 seconds with 30 second intervals on ice.

The EPO (eosinophil peroxidase, an eosinophil protein used as a marker of eosinophil presence) assay consisted of determining the levels of EPO in the lung tissue (or supernatant of BAL fluid) from each individual guinea pig sample. 50 ul of the "sample solution" consisting of 375 ul PBS (pH 7, RT) + 25 ul 0.05 M TRIS-HCL containing 2 % Triton (pH 8, RT) + 50 ul of sonicated lung lobe was added to 860 ul 0.05 M TRIS-HCL containing 0.1 % Triton (pH 8, RT) in combination with 8.5 ul mM 0-phenylenediaminedihydrochloride (OPD). To start the reaction, 1 ul of 30 % hydrogen peroxide was added to the cuvette. The optical density reading was measured spectrophotometrically over a 4 minute time interval at 490 nm in a Beckman Du-64 spectrophotometer.

Table 5
Inhibition of Ovalbumin-Induced Lung Eosinophilia in the Guinea Pig

Treatment	Drug mg/kg	EPO Concentration in the Lung[b,c] ($\chi \pm$SE)	% Inhibition
Group 1:			
Cmpd 1 Aerosol Inhalation			
Non-Ovalbumin Control	0.0	0.0312 $\pm$ 0.005	
Ovalbumin Challenged	0.0	0.2959 $\pm$ 0.035	
Drug + Ovalbumin Challenged	0.003	0.2620 $\pm$ 0.116	13%
	0.01	0.1806 $\pm$ 0.035*	44%
Group 2:			
Cmpd 1 Intraperitoneal Administration			
Non-Ovalbumin Control	0.0	0.0338 $\pm$ 0.004	
Ovalbumin Challenged	0.0	0.3268 $\pm$ 0.046	
Drug + Ovalbumin Challenged	0.003	0.2435 $\pm$ 0.0515	28%
	0.01	0.1690 $\pm$ 0.053*	54%
	0.03	0.1693 $\pm$ 0.060*	54%
	3.0	0.0580 + 0.018*	92%
Group 3:			
Cmpd 2 Oral Administration			
Non-Ovalbumin Control	0.0	0.0203 $\pm$ 0.008	
Ovalbumin Challenged	0.0	0.2307 $\pm$ 0.010	
Drug + Ovalbomin Challenged	0.001	0.1862 $\pm$ 0.030	19%
	0.01	0.1181 $\pm$ 0.020*	49%
	0.1	0.0118 $\pm$ 0.005*	95%
	1.0	0.0084 + 0.005*	96%

*= Significant difference from ovalbumin control group at α=0.05

The above studies indicate that the IRM compounds of the present invention can be used for treatment of TH2 mediated diseases by inhibiting TH2 immune responses, and suppressing IL-4

and IL-5 induction and eosinopilia. Examples of such diseases include asthma, allergy, atopic dermatitis, early HIV disease, infectious mononucleosis, and systemic lupus erythematosis. There is also an association with an increased TH2 response in Hodgkin's and non-Hodgkin's lymphoma as well as embryonal carcinoma. Moreover, the ability of the IRM compounds of the present invention to inhibit TH2 response and augment TH1 response indicates that these compounds will be useful in treating parasitic infections, for example, cutaneous and systemic leishmaniasis, Toxoplasma infection and Trypanosome infection, certain fungal infections, for example Candidiasis and Histoplasmosis, and intracellular bacterial infections, such as leprosy and tuberculosis. Studies in mice infected with leishmania major have shown that a TH1 response correlates with resistance, whereas a TH2 response correlates with susceptibility. Also studies in mice have shown that parasites that live in macrophages, for example, leishmania major, are killed when the host cells are activated by interferon-γ, which is known to be a TH1 cell product. In mice infected with candida and histoplasma, it is known that a TH1 response correlates with resistance, whereas a TH2 response correlates with susceptibility.

Accordingly, from all of the above, it is apparent that the imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines of the present invention are useful for treating TH2 mediated and other related diseases. Although the invention has been presented in terms of preferred embodiments and specific examples, there is no intention to limit the invention to such embodiments and examples. Additionally, it is intended that the disclosures of all the documents referred to in the preceding disclosure are expressly incorporated herein by reference.

CLAIMS

We claim:

1. A method of treating a non-viral and non-tumor, TH2 cell mediated disease comprising administering an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines in an amount effective to inhibit TH2 cell mediated immune response, with the proviso that said disease is other than eczema.

2. The method of claim 1, wherein said disease is a parasitic infection.

3. The method of claim 1, wherein said disease is a bacterial infection.

4. The method of claim 1, wherein said disease is a fungal infection.

5. The method of claim 1, wherein said disease is selected from the group consisting of asthma, allergy, leprosy, systemic lupus erythematosis, Ommen's syndrome, leishmaniasis, toxoplasma infection, trypanosome infection, candidiasis, and histoplasmosis.

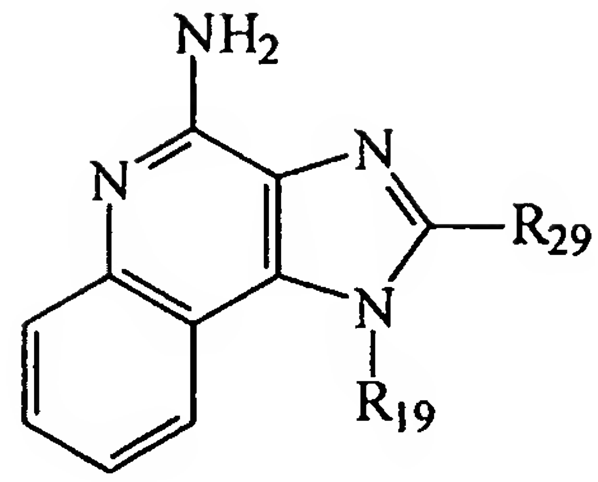
6. The method of claim 1, wherein said disease is selected from the group consisting of asthma and allergic rhinitis.

7. The method of claim 1, wherein said compound is administered via oral or nasal inhalation.

8. The method of claim 1, wherein said compound is administered via a topical cream or gel.

9. The method of claim 1, wherein said compound is selected from the group consisting of 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol and 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

10. The method of claim 1, wherein said immune response modifier compound is a compound of Formula IX



IX

or a pharmaceutically acceptable salt thereof,

wherein

R_{19} is selected from the group consisting of alkyl containing one to six carbon atoms and hydroxyalkyl containing one to six carbon atoms; and

R_{29} is selected from the group consisting of hydrogen, alkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, and hydroxyalkyl containing one to four carbon atoms.

11. The method according to Claim 10, wherein said R_{19} is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

12. A method according to Claim 10, wherein said R_{29} is selected from the group consisting of hydrogen, methyl, butyl, hydroxymethyl, ethoxymethyl, and methoxymethyl.

13. A method of inhibiting induction of IL-4 and/or IL-5 cytokines to treat a non-viral and non-tumor disease comprising administering an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines in an amount effective to inhibit said IL-4 and/or IL-5 cytokines, with the proviso that said disease is other than eczema.

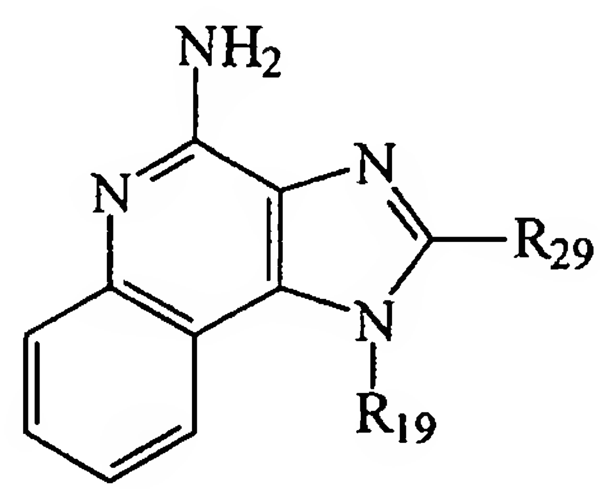
14. A method of treating eosinophilia comprising administering an immune response modifier compound selected from the group consisting of imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, and 1,2-bridged imidazoquinoline amines in an amount effective to inhibit said eosinophilia, with the proviso that said disease is other than eczema.

15. The method of claim 14, wherein said compound is administered via oral or nasal inhalation.

16. The method of claim 14, wherein said compound is administered via a topical cream or gel.

17. The method of claim 14, wherein said compound is selected from the group consisting of 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol and 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

18. The method of claims 14, wherein said immune response modifier compound is a compound of Formula IX



IX

or a pharmaceutically acceptable salt thereof,

wherein

R_{19} is selected from the group consisting of alkyl containing one to six carbon atoms and hydroxyalkyl containing one to six carbon atoms; and

R_{29} is selected from the group consisting of hydrogen, alkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, and hydroxyalkyl containing one to four carbon atoms.

19. The method according to Claim 18, wherein said R_{19} is 2-methylpropyl or 2-hydroxy-2-methylpropyl.

20. A method according to Claim 18, wherein said R_{29} is selected from the group consisting of hydrogen, methyl, butyl, hydroxymethyl, ethoxymethyl, and methoxymethyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/19990

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VARNER ET AL: "effects of imiquimod on post-viral asthma-like syndrome" J OF ALLERGY AND CLINICAL IMMUNOLOGY, vol. 99, no. 1(2), 26 February 1996, page s127 XP002055521 abstract 516 ---	1,7, 9-12,14, 15,17-20
A	EP 0 193 329 A (BEECHAM GROUP PLC) 3 September 1986 see page 3; figure I see page 9, left-hand column, line 8-9 see page 9, left-hand column, line 26-27 -----	1,5-8, 13-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 1998	26. 03. 98
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Trifilieff-Riolo, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/19990

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of
--------------------the following reasons:

Claims Nos.: 1-20
----

because they relate to subject matter not required to be searched by this Authority, namely:

see remarks

Claims Nos.: 1-8, 13-16

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the large number of compounds defined by the general description used in claims 1-8 and 13-16, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and /or the compounds mentioned in the claims and to the general idea underlying the application (see Guidelines, chapter III, par. 2.3).

Remark : Although claims 1-20
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/US 97/19990

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0193329 A	03-09-86	AU 5379386 A	28-08-86
		DK 79986 A	23-08-86
		JP 61225184 A	06-10-86
		US 4837238 A	06-06-89